Page 4 of the specification has been amended to incorporate by reference information from the abstract of the grandparent patent Application No. 08/714,313 (which issued as US Patent No. 5,994,294 on November 30, 1999) to which the present application claims priority.

The last paragraph on page 46 of the specification has been editorially amended.

No issues of new mater should arise and entry of the amendment is respectfully requested.

II. Restriction Requirement

In response to the Restriction Requirement of March 22, 2001, Applicants elected the Examiner's Group VI with traverse. In the Office Action dated June 29, 2001, the Examiner made the restriction requirement final. In view thereof, Applicants are filing concurrently herewith a Petition from Requirement for Restriction Under 37 C.F.R. § 1.144.

Applicants respectfully request that the Petition be forwarded to the Group Director for timely consideration.

III. Rejection under 35 U.S.C. §112, First Paragraph

Claims 61-65 are rejected under 35 U.S.C. §112, first paragraph, as containing new matter. The Examiner asserts that the original specification and claims do not support treating "female impotence" presented in claims 61-65.

Applicants respectfully traverse the rejection and respectfully submit that the term "female impotence" is not new matter since this term was clearly described in grandparent Application No. 08/714,313 filed September 18, 1996 (issued as US Patent No. 5,994,294).

The specification indicates that all the cited applications are incorporated by reference (specification at page 73, lines 5-6). In view thereof, Applicants have amended the paragraph in the specification at page 4, lines 14-24 to refer to "human impotence," which was described in the Abstract of priority grandparent Application No. 08/714,313 filed September 18, 1996, issued as U.S. Patent No. 5,994,294. Moreover, one skilled in the art would recognize that the term "human impotence" includes "male impotence" and "female impotence."

The Declaration for the present application (which was a copy of the Declaration from parent Application No. 09/145,143 filed September 1, 1998) filed on January 5, 2000, specifically refers to the priority grandparent Application No. 08/714,313 filed September 18, 1996. Hence, the terms "human impotence," "female impotence," and "male impotence" do not constitute new matter.

In further support of their position, Applicants are submitting herewith a copy of a Declaration under 37 CFR § 1.132 by Gorm M. Wagner, an expert in the field of human sexuality, that was filed in parent Application No. 09/145,143. The Wagner Declaration shows that one skilled in the art would recognize that the term "human impotence" in grandparent Application No. 08/595,732 includes male impotence and female impotence. *See* Wagner Declaration at Paragraph Nos. 4-10. The Wagner Declaration also shows that in 1996 one skilled in the art used the term "impotence" to mean and include the now commonly used term "sexual dysfunction." *See* Wagner Declaration at Paragraph Nos. 11-12.

In view of the above, Applicants respectfully submit that there is no new matter in the claims, and respectfully request that the rejection under § 112, first paragraph, be withdrawn.

IV. Rejection under 35 U.S.C. § 103

A. Related U.S. Patents

The PTO has issued patents directed to methods for treating female sexual dysfunctions (e.g., female impotence) using compounds that were previously known to be effective for treating male sexual dysfunctions. Thus, the PTO has already established that the use of compounds to treat male sexual dysfunctions does not render *prima facie* obvious the use of the same compounds to treat female sexual dysfunctions.

In particular, Applicants refer to U.S. Patent No. 5,945,117 entitled "Female Sexual Dysfunction," a copy of which is attached in the Information Disclosure Statement filed herewith. Claim 1 of U.S. Patent No. 5,945,711 recites:

> A method of ameliorating sexual dysfucntion in a human female which comprises administering to said human female apomorphine or a pharmaceutically acceptable acid addition salt thereof as a sublingual dosage form and in an amount sufficient to increase intraclitoral blood flow and vaginal wall flow on stimulation of said human female but less than the amount that induces substantial nausea.

The U.S. Patent Office found the claims of U.S. Patent No. 5,945,117 to be patentable over U.S. Patent No. 5,770,606, entitled "Dosage Forms and Methods for Ameliorating Male Erectile Dysfunction," a copy of which is attached in the Information Disclosure Statement filed herewith. Claim 1 of U.S. Patent No. 5,770,606 recites:

> A method of ameliorating erectile dysfunction in a psychogenic male patient which comprises administering to said patient apomorphine or a pharmaceutically acceptable acid addition salt thereof sublingually prior to sexual activity, and in an amount sufficient to induce an erection adequate for vaginal penetration but less than the amount that induces nausea.

During the prosecution of U.S. Patent No. 5,945,117, both U.S. Patent No. 5,770,606 and Gioco (U.S. Patent No. 5,565,464) were considered by the PTO. Additionally, Applicants for U.S. Patent No. 5,945,117 did not present to the PTO any data showing the unobviousness of female dysfunction over male erectile dysfunction comprising adminstration of apomorphine.

Thus, the PTO found claims directed to methods for treating female sexual dysfunction with apomorphine (i.e., U.S. Patent No. 5,945,711) to be patentable over methods for treating male sexual dysfunction with apomorphone (i.e., US Patent No. 5,770,606) in view of Gioco (US Patent No. 5,565,464).

Applicants also refer to U.S. Patent No. 5,877,216, entitled "Treatment of Female Sexual Dysfunction," which was cited in the Information Disclosure Statement filed on January 5, 2000. This patent has claims directed to methods for treating female sexual dysfunction using naturally occurring prostaglandins and synthetic prostaglandin derivatives.

The use of prostaglandins to treat male erectile dysfunction was well known in the art, as described, for example, in U S. Patent Nos. 5,708,031 and 5,718,917, copies of which are attached in the Information Disclosure Statement filed herewith. Additionally, two products containing prostaglandin E_1 for the treatment of male erectile dysfunction have been approved by

the U.S. Food and Drug Administration (i.e., CAVERJECT®, Pharmacia & Upjohn Company, Kalamazoo, MI, and MUSE®, Vivus Incorporated, Mountain View, CA).

The Applicants for U.S. Patent No. 5,877,216 did not present to the Patent Office any data showing the unobviousness of female dysfunction over male erectile dysfunction by administering prostaglandins. In fact, the PTO found the claims in U.S. Patent No. 5,877,216 to be patentable over the prior art including Gioco (U. S. Patent No. 5,565,464).

Thus, the PTO found claims directed to methods for treating female sexual dysfunction with prostaglandins (i.e., U.S. Patent No. 5,877,216) to be patentable over methods for treating male sexual dysfunction with prostaglandins in view of Gioco (US Patent No. 5,565,464).

Thus, the PTO has clearly established a precedent that claims directed to methods for treating female sexual dysfunctions are patentably distinct from methods for treating male sexual dysfunctions with the same compounds.

B. Rejection under 35 U.S.C. § 103

Claims 35-46[1] are rejected under 35 U.S.C. § 103 as being obvious over Stamler et al (U.S. Patent No. 5,380,758) in view of Gioco et al (U.S. Patent No. 5,565,466).

Applicants respectfully traverse the rejection and respectfully submit that there is no motivation to combine the cited references to arrive at the presently claimed invention

Stamler describes S-nitrosothiol compounds that relax vascular and non-vascular smooth muscle, such as airway, gastrointestinal, bladder, uterine and corpus cavernosal. As pointed out by the Examiner, Stamler does not disclose or suggest the use of S-nitrosothiols to treat female sexual dysfunctions, and does not provide motivation for one to use S-nitrosothiols to treat female sexual dysfunctions.

Gioco merely teaches one similarity between male and female sexual response, i.e., engorgement. At column 4, lines 45-50 (emphasis added), Gioco teaches:

[1] Applicants assume this is typographical error and that the Examiner intended to refer to pending claims 61-65.

> ***While there are obvious differences*** in the sexual response between men and women, ***one common aspect*** of the sexual response is erectile response. The erectile response in both males and females is result of engorgement of the erectile tissues of the genitalia with blood in response to sexual stimulation (physical, psychological, or both).

Applicants respectfully submit that the female sexual response is more complex -- both physically and mentally -- than the male sexual response, and that one commonality does not provide any reason for one to believe that the treatments would be the same.

Female sexual response involves not only clitoral erection, vaginal blood flow and engorgement, but also other factors, such as, for example, vaginal length change, vaginal luminal pressure, vaginal lubrication, vaginal pH, hormonal shifts, and the like. *See,* for example, Berman et al., *Urology*, 54:385-391 (1999); Levin, *Exp. Clin. Endocrinol.*, 98(2):61-69 (1991); Halvorsen et al., *J. Am. Board Fam Pract*, 5:51-61 (1992), copies of which are attached in the Information Disclosure Statement filed herewith. Vaginal and/or periuethral glans stimulation is also implicated in female sexual response. *See*, for example, Levin at page 65, line 32 to page 67, line 4.

Many treatments for female sexual dysfunctions have been inappropriately based upon studies in males, and many aspects of female sexual dysfunction have never been previously examined. *See*, for example, Goodnow, Chicago Tribunes, Dec 14, 1997, column 1, lines 39-55, copy of which is attached in the Information Disclosure Statement filed herewith.

As acknowledged by Gioco, and supported by the cited art of record, ***there are many differences between male and female sexual responses***. One skilled in the art would not conclude that the treatment for male impotence or male sexual dysfunction would be the same as the treatment for female impotence or female sexual dysfunction. Additionally, one skilled in the art would not conclude that a compound that results in vasodilation, increased blood flow and engorgement to the genitalia would also result in vaginal length change, vaginal luminal pressure, vaginal lubrication, vaginal pH, hormonal shifts, etc., and effect other factors that are responsible for female sexual dysfunctions or females impotence. Again, Gioco does not disclose or suggest that a compound that results in vasodilation, increased blood flow and engorgement to the genitalia would also result in vaginal length change, vaginal luminal

pressure, vaginal lubrication, vaginal pH, hormonal shifts, etc. and effect other factors that result in female impotence or female sexual dysfunctions.

Thus, Stamler in combination with Gioco does not provide any motivation for one to arrive at the presently claimed methods of treating female impotence by administering S-nitrosothiol compounds.

In view of the above, Applicants respectfully submit that the presently claimed invention is unobvious over the cited references, and respectfully request that the rejection under 35 U.S.C. § 103 be withdrawn.

V. First Obviousness-Type Double Patenting Rejection

Claims 61-65 are rejected under the judicially created doctrine of obviousness-type double patenting over claims 8-11 of co-pending Application No. 09/354,424 in view of Stamler et al (U.S. Patent No. 5,380,758) and Gioco et al (U.S. Patent No. 5,565,466).

Applicants submit herewith an executed Terminal Disclaimer which refers to U.S. Application No. 09/354,424. In view thereof, Applicants respectfully request that the obviousness-type double patenting rejection be withdrawn.

VI. Second Obviousness-Type Double Patenting Rejection

Claims 61-65 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting over claims 20-66 of co-pending Application No. 09/280,540, in view of Stamler et al (U.S. Patent No. 5,380,758) and Gioco et al (U.S. Patent No. 5,565,466).

Claims 20-66 of co-pending Application No. 09/280,540, are directed to compositions comprising α-adrenergic receptor antagonists, such as imidazoline compounds, **in combination with** nitric oxide donor compounds (i.e. a compound that donates, transfers or releases nitric oxide, elevates levels of endogenous endothelium-derived relaxing factor or stimulates endogenous nitric oxide synthesis which includes S-nitrosothiol compounds) and their methods of use for the treatment of sexual dysfunctions. The claims of the present application are directed to methods of treating female impotence with S-nitrosothiol compounds (i.e., a nitric oxide donor compound) **alone**. Hence, the claims of the present application and co-pending Application No. 09/280,540 are directed to different and patentably distinct subject matter.

As discussed above and incorporated by reference herein, Stamler in combination with Gioco does not provide any motivation or suggestion for one to arrive at the presently claimed methods of treating female impotence by administering of S-nitrosothiol compounds. Hence, the claims of the present invention are unobvious over the combined references.

In view of the above, Applicants respectfully request that the provisional double patenting rejection, be withdrawn.

VII. Third Obviousness-Type Double Patenting Rejection

Claims 61-65 are rejected under the judicially created doctrine of obviousness-type double patenting over claims 35-56 of co-pending Application No. 09/306,809, in view of Stamler et al (U.S. Patent No. 5,380,758) and Gioco et al (U.S. Patent No. 5,565,466).

Claims 35-56 of co-pending Application No. 09/306,809, are directed to compositions comprising nitrosated/nitrosylated α-adrenergic receptor antagonists of Forumla III alone or **in combination with** nitric oxide donors (i.e. a compound that donates, transfers or releases nitric oxide, elevates levels of endogenous endothelium-derived relaxing factor or stimulates endogenous nitric oxide synthesis which includes S-nitrosothiol compounds) and their methods of use for the treatment of female sexual dysfunctions. The claims of the present application are directed to methods for the treatment of female impotence with S-nitrosothiol compounds **alone**. Hence, the claims of the present application and co-pending Application No. 09/306,805 are directed to different and patentably distinct subject matter.

As discussed above and incorporated by reference herein, Stamler in combination with Gioco does not provide any motivation or suggestion for one to arrive at the presently claimed methods of treating female impotence by administering of S-nitrosothiol compounds. Hence, the claims of the present invention are unobvious over the combined references.

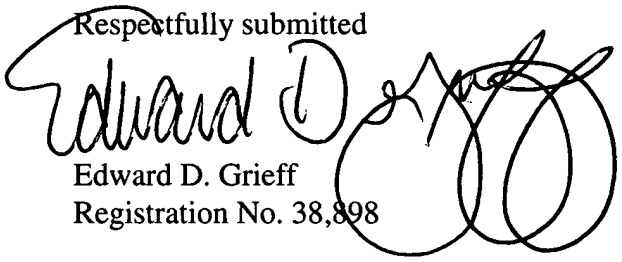
In view of the above, Applicants respectfully request that the provisional double patenting rejection, be withdrawn.

XI. Conclusion

Applicants respectfully request reconsideration and allowance of pending claims 61-65.

Examiner Celsa is encouraged to contact the undersigned at 202-942-8453 concerning any questions about the present application.

Respectfully submitted



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